REMARKS

Applicants solicit favorable reconsideration and a notice of allowance following entry of this Amendment.

Applicants acknowledge the Examiners' courtesy during the telephone discussion reported in the prior Rule 133 Statement. It is very much appreciated.

Applicants have canceled the non-elected claims with neither prejudice nor disclaimer.

Applicants have made minor editorial amendments to claim 94 in an effort to improve readability. Applicants believe their claim 94 is now free of the 35 U.S.C. 112(2) rejection. If, upon further review, the Examiners consider a matter may need clarification, they are kindly invited to contact the undersigned.

Applicants have amended claim 110 to make it an independent claim. As presented, it is intended to present a clean independent claim inasmuch as claim 110 and is drawn from previously presented claim 94 and the specification, including Examples 5 and 6, as examples. Applicants believe the amended claim satisfies the requirements of 35 U.S.C. 112(2). Applicants suggest claim 110 is also free of the art of record.

If, upon further review, the Examiners consider a matter in claim 94 or claim 110 might need clarification, they are kindly invited to contact the undersigned.

Amended claims 139 and 141 depend from amended claim 110.

Amended claim 138 depends from claim 94.

Applicants' novel and innovative approach is to introduce desired properties with minimal change to the protein or peptide. Specifically to perform quantitative structure function analysis using gradually increasing modification, monitoring this modification in a mild manner,

using protease treatment and mass spectrometry and assaying biological activity. The monitoring can by way of example be carried out with denaturing electrophoresis and/or electrospray mass spectrometry. The protease treatment and mass spectrometry tests are suitable for locating and determining the nature of the modification.

Applicants respectfully submit their claims particularly point out and distinctly claim the subject matter they regard as their invention(s).

Applicants believe that the language "mild and sensitive nature" is would be understood by persons who are skilled in the art. The claim need not have details akin the numerical precision in order to comply with Section 112(2). The Examples in the specification provide guidance. Applicants respectfully invite attention to the literature appended to their previously filed Rule 133 Statement. It is understood from the interview that the Examiners that this ground of rejection would be favorably reconsidered.

As amended, claim 110 overcomes the rejection leveled against such claim based on the word "substrate." Reconsideration and allowance of claim 110 is therefore courteously solicited.

Applicants respectfully solicit reconsideration and withdrawal of the rejection over the Witowska document.

It is understood that the Examiners are of the view that the "claims are drawn to a method for structure function analysis research on biologically active proteins or peptides, comprising gradual chemical modification of a protein or peptide, monitoring the modification reaction using a method of electrospray mass spectrometry, protease treatment, mass spectrometry and or assaying biological activity of the modified product."

Applicants' method is a means by which structure function analysis is used to produce an antagonist or superagonist. It is not a just a method to perform analysis. Applicants indeed

obtain superagonists and antagonists, in contrast to Witowska who just analyzes variants of Hemoglobin by mass.

In fact, no study of the function is performed at all by Witowska as is illustrated by the phrasing at page 240; lines 18-21 wherein it is stated that:

> "*In summary, ...spectrometer can streamline variant Hb identification..... and determining their molecular masses and amino acid sequences.*"

Thus, only variant identification, molecular mass determination and determination of amino acids sequence is involved.

Thus, Applicants respectfully submit their method is novel over Witowsky because: with their invention one obtains superagonists and/or antagonists; and with their invention one studies the (biological) function of the obtained products.

Moreover, in their invention (1) HPLC is eliminated whereas Witowsky uses HPLC (See title), thereby including unpredictable losses and excessive denaturation; (2) they perform quantitative structure function analysis in contrast to the method of Witowsky; and (3) they perform gradual modification in stead of complete modification as is illustrated at page 229; lines 30-34: "*reduction/alkylation volumes were ....100 mM iodoacetamide.... And subsequently.....in presence of an excess of alkylation and denaturing reagents....*" Finally, in their invention Applicants use of EDTA as a chelating agent (agent to remove a metal ion), and they do not require urea as a chelating ion, but to make the structure more accessible for the EDTA and Iodo Acetic acid.

Applicants therefore respectfully solicit favorable reconsideration and withdrawal of this rejection.

Applicants respectfully traverse the rejection of claims 94-100, 106, 109, and 138 over the Knepper et al. reference (Knepper et al (Biochemistry, 1992Vol 31, p. 11651-11659)). As presently understood, the Examiners are of the view that the "claims are drawn to a method for quantitative structure function analysis research on biologically active proteins or peptides, comprising gradual chemical modification of a protein or peptide, monitoring the modification reaction using a method of electrospray mass spectrometry, protease treatment, mass spectrometry and or assaying biological activity of the modified product."

Applicants' method is a means by which structure function analysis is used to produce an antagonist or superagonist. It is not a just a method to perform analysis. Applicants indeed obtain superagonists and antagonists in contrast to Knepper who just used mass spectrometry to determine primary structural features of mouse Il-3. This is depicted for instance on page 11657; Discussion, first line:

> "*In the present study LSIMS analyses in combination with proteolytic digestion techniques were used to determine primary structural features of IL-3.*"

Applicants' method is also novel over Knepper because (1) they obtain superagonists and/or antagonists; and (2) they can also confirm via studies the (biological) function of the obtained products. Moreover, (3) in Applicants' invention HPLC is not necessary whereas Knepper uses HPLC (see page 11652, right column lines 18-25), thereby including unpredictable losses and excessive denaturation.

Furthermore, in Applicants' invention (4) they perform quantitative structure function analysis in contrast to the method of Knepper; (5) they can effect and study a gradual modification instead of rapid, complete modification and separation as is illustrated in the

Knepper reference at page 11652, left column last 4 lines, wherein it is stated that the (completely) deglycosylated mouse IL-3 is isolated for further study:

> "*Separation of the deglycosylated IL-3 from the released oligosaccharides was carried out using an Amicon Centricon filtation system. Further purification was carried out by C18 Reversed Phase HPLC.*"

Applicants respectfully traverse the rejection of claims 94-100, 106, and 109 over the Acone reference. As presently understood, the Examiners are of the view that the "claims are drawn to a method for quantitative structure function analysis research on biologically active proteins or peptides, comprising gradual chemical modification of a protein or peptide, monitoring the modification reaction using a method of electrospray mass spectrometry, protease treatment, mass spectrometry and or assaying biological activity of the modified product."

Applicants' method is a means by which structure function analysis is used to produce an antagonist or superagonist. It is not a just a method to perform analysis. Applicants indeed obtain superagonists and antagonists in contrast to Arcone who just used mass spectrometry to characterize the structure of a purified IL-6. This is depicted in the title and for instance on page 547; Conclusions, fourth to sixth line:

> "... structural characterization has been performed by mass spectrometric mapping."

Thus, Applicants' method is novel over the Arcone reference because (1) Applicants' invention enables a person skilled in the art to obtain superagonists and/or antagonists; and (2) they can produce and study the (biological) function of the obtained products.

Moreover, (3) in Applicants' method, chromatography is not necessary whereas Arcone uses FPLC (see page 542, left column lines 10-5 from below), and

HPLC analysis (heading in the right column), thereby including unpredictable losses and excessive denaturation.

Furthermore, in Applicants' invention quantitative structure function analysis is performed in contrast to the method of Arcone who describe neither function analysis nor quantitative structure because there is no apparent description, for instance, of the relation between the several structural features he found, and the activity.

Applicants respectfully traverse the rejection of claims 94-100, 106, and 109 over the Woods reference. As presently understood, the Examiners are of the view that the "claims are drawn to a method for quantitative structure function analysis research on biologically active proteins or peptides, comprising gradual chemical modification of a protein or peptide, monitoring the modification reaction using a method of electrospray mass spectrometry, protease treatment, mass spectrometry and or assaying biological activity of the modified product."

Applicants' method is a means by which structure function analysis is used to produce an antagonist or superagonist. It is not a just a method to perform analysis. Applicants indeed obtain superagonists and antagonists in contrast to Woods who used radioactivity to characterize epitopes on Haemoglobin. This is also depicted in the Woods Abstract on the first page wherein it is stated that:

> "The binding sites .....are characterized,.., by a combination of tritium exchange labelling and sequential degradation and analysis of tritiated fragments under ...."

Applicants' method is also novel over Woods because (1) with Applicant's method they obtain obtains superagonists and/or antagonists; (2) they can produce and study the biological function of the obtained products (quantitative and function analysis).

Moreover, in Applicants' invention any preperative separation is not necessary and, like HPLC, can be eliminated whereas Woods does not (see page 5 Claim 1 step e), thereby including unpredictable losses and excessive denaturation.

Furthermore, in Applicants' method, the production and analyses are performed without complicated procedures that involve the use of radioactive substances.

Applicants respectfully traverse the rejection of claims 94-100, 106, 109, and 138 over the Bradford-Goldberg reference. As presently understood, the Examiners are of the view that the "claims are drawn to a method for quantitative structure function analysis research on biologically active proteins or peptides, comprising gradual chemical modification of a protein or peptide, monitoring the modification reaction using a method of electrospray mass spectrometry, protease treatment, mass spectrometry and or assaying biological activity of the modified product." It elsewhere seems the Examiners are of the view that Bradford-Goldberg et al disclose a method of quantitative structure function analysis of a modified Il-3.

Applicants respectfully solicit reconsideration and withdrawal of this rejection and its rationale.

As to the reference, as depicted in the first lines of its Abstract: "The invention relates to recombinant human Interleukin-3 variant and mutant proteins..." The Abstract does not describe the present method(s).

Applicants' method is therefore considered novel over this reference because (1) Applicants use gradual chemical modification; (2) Applicants produce the product and perform quantitative structure and function analysis to confirm the production of the modified protein or peptide.

Moreover, in Applicants' invention, (3) preperative separation is not necessary and is eliminated whereas Bradford-Goldberg uses fractionation, extraction of refractile bodies, refolding, and further purification steps are taught. Consequently, Bradford-Goldberg includes unpredictable losses and excessive denaturation.

Accordingly, Applicants respectfully solicit reconsideration and withdrawal of the rejection over the Bradford-Goldberg reference.

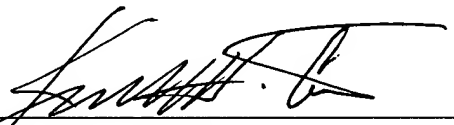
Lastly, Applicants respectfully solicit reconsideration and withdrawal of the obviousness rejection, in which the Weber-Rosnak reference is included with the other references (Office Action, at page 8). It is respectfully submitted that the references would not have led a person of ordinary skill in the art to the present claimed inventions, even if they were combined, which they wouldn't have been without impermissible hindsight, and furthermore the addition of the Weber-Rosnack reference would ***not*** have supplied the information, teaching, suggestion, or the like to such a person in the direction of Applicants' invention. Indeed, as to the other references applied as well as the Weber-Rosnack reference itself, there does not appear to be a quantitative structure-function relationship reported or disclosed as performed in any of the applied documents; mild monitoring is not used; no gradual chemical modification is performed in combination with a study of activity; and no introduction of antagonistic activity or superagonistic activity can be reasonably assumed in combination with a catalytic center.

CONCLUSION

Applicants courteously solicit favorable reconsideration and a notice of allowance.

If the Examiners have any questions, they are kindly invited to telephone the undersigned.

Respectfully submitted,



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